Strategy and tactics of marijuana research

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Summary: Before undertaking marijuana research, certain demands must be met in the following areas: educational and health facilities, the legal position, funding, Food and Drug Directorate regulations and law enforcement. Methodological problems include those concerned with pharmacology, nature of effect, set, setting, subjects, dependent variables and controls. The second portion of this paper describes the methodology and findings of a clinical study of 81 volunteers, selected according to specified criteria, screened psychiatrically and psychologically, then assigned to one of seven experimental groups. Dosage and smoking procedure were standardized for both marijuana and placebo. The experience was evaluated subjectively by the volunteers at the end of each experimental session and again on the following morning.

Résumé: *La stratégie et la tactique adoptées pour les recherches sur la marijuane*
Avant d'entreprendre des recherches sur la marijuane, certains problèmes doivent être mis au point dans les domaines suivants: ressources en matière d'éducation et de soins, lois en vigueur, subsides, Administration des Aliments et des Drogues, application de la loi. Parmi les problèmes méthodologiques, on peut citer: la pharmacologie du produit, la nature de son effet, les attentes des sujets, milieu de l'expérience, sujets de l'étude, variables pertinentes et témoins. La seconde partie du présent article décrit la méthodologie utilisée et les constatations faites au cours de l'étude clinique de 81 volontaires, choisis selon des critères spécifiés, évalués au double point de vue psychiatrique et psychologique, puis affectés à l'un des sept groupes expérimentaux. Les doses de marijuane et de placébo et les méthodes de fumer ont été standardisées. L'expérience a été estimée subjectivement par les volontaires à la fin de chaque séance expérimentale et le lendemain matin.

Study assisted under National Health Grant 610-25-1
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Weil, Zinberg and Nelsen[1] pointed out in 1968 that research on marijuana is fraught with a large number of legal and attitudinal hurdles and obstacles. The situation they described still obtains today. Accordingly it might be helpful to provide first-hand information and data regarding the nature of such obstacles and, even more important, the ways and means of meeting the necessary demands in order to embark on marijuana research. Table I outlines the channels — university, medico-legal, funding, Food and Drug, and law enforcement — that one must go through before beginning a systematic inquiry on marijuana.

A model for marijuana research

In addition to legal and logistical problems, there are many inherent methodological problems that must be faced in research on marijuana. In spite of the almost phrenetic reporting on the symbols of social conflict — psychoactive drugs, particularly marijuana — during recent years, a good deal of literature in the field is still replete with fear, mythology and overgeneralization, rather than systematic inquiry. Generalizations, in order to be scientifically valid for humans, should be based on human rather than, or in addition to, preclinical research on animals. While animal behaviour is based upon anthropomorphic assumptions and may be valid for biochemical and neurophysiological processes, it does not follow that animal behaviour and human behaviour are similarly affected by psychoactive drugs.[2] Secondly, clinical-experimental observation should counterbalance anecdotal-descriptive reports, for the latter are often confounded by retrospective falsification of the examinee and biases of the examiner. Thirdly, findings must relate to the socio-cultural matrix. Fourthly, findings should be reproducible.

A model is proposed which would permit the planning of more meaningful research on marijuana and, equally important, would provide bench marks for critical evaluation of reports and literature on this subject. The components of such a model and the associated methodological problems are as follows:

(1) *Pharmacology* — Unresolved problems include:

source and composition; chemical structure; biological actions; toxic effects; routes of administration; absorption; physiological fate; distribution and excretion; duration of action; tolerance, reverse tolerance and cross-tolerance; therapeutic potential; and dose-response with standardized amounts of Δ^9-THC as well as response to amounts usually smoked by subjects (subjective-high). Comparative assessment of research is well-nigh impossible unless there is a specification of pharmacological variables, particularly those variables which relate to potency of Δ^9-THC.

(2) *Nature of effect* — Most clinical studies to date have dealt with short-term effects. Statements regarding long-term effects invariably derive from anecdotal reports that may not be related to the sociocultural matrix, or from retrospective clinical studies where the design and inferences are highly suspect.

(3) *Set* — The expectancies, attitudes and motivation of subjects, as well as learned skills for modifying the drug experience, should be taken into account. The expectancies and attitudes of examiners may also influence results.

(4) *Setting* — Anecdotal statements about the effects of marijuana in social settings, using an illicit agent, may be misleading. Rigid systematic clinical inquiry in a sterile laboratory environment may also result in artefact. In the design of research into the effects of marijuana, one should accordingly strive to create a setting that is socially and clinically relevant.

(5) *Subjects* — Interpretation of drug effects should take into account the following: physical health; personality characteristics; possible sex differences; and drug history including light, moderate or heavy usage of prescribed and non-prescribed drugs.

(6) *Dependent variables* — The most obvious basic requirements for drug evaluation are stable and reproducible baselines against which to assess drug-correlated changes. Objective dependent variables are urgently needed to assess changes due to psychoactive drug effects, and these would include: cognitive-perceptual measures; personality measures; rating scales and behavioural inventories; and electrophysiological measures. Subjective drug effects questionnaires are useful adjuncts. In all instances of drug evaluation there should be a clear-cut specification as to whether the effects being measured are short-term or long-term.

(7) *Controls* — Serious studies on drug effects should include controls, specifically one placebo group or condition.

Clinical study at U.B.C.

Criteria for volunteers and screening procedure

All subjects were volunteers who met the following criteria: (1) age between 19 and 31; (2) light and restricted use of psychoactive drugs (24 subjects — 15 men and 9 women — had experimented with psychoactive drugs other than marijuana or hashish at some time, but not during the past year); (3) not on any form of prescribed drug regimen; (4) good physical health; and (5) no signs of serious personality disorder. There was no advertising for volunteers and interested individuals became aware of the project through the grapevine.

Prospective subjects were initially interviewed by the project coordinator, informed about the general nature of the experiment, given an opportunity to ask relevant questions regarding the project, and were then given the opportunity of volunteering for the study. Enough volunteers of each sex were chosen to yield a male: female ratio of approximately 1:1. Those volunteers who satisfied all of the above criteria were then interviewed by the psychiatrist. The results of the psychiatric interviews will be reported separately.

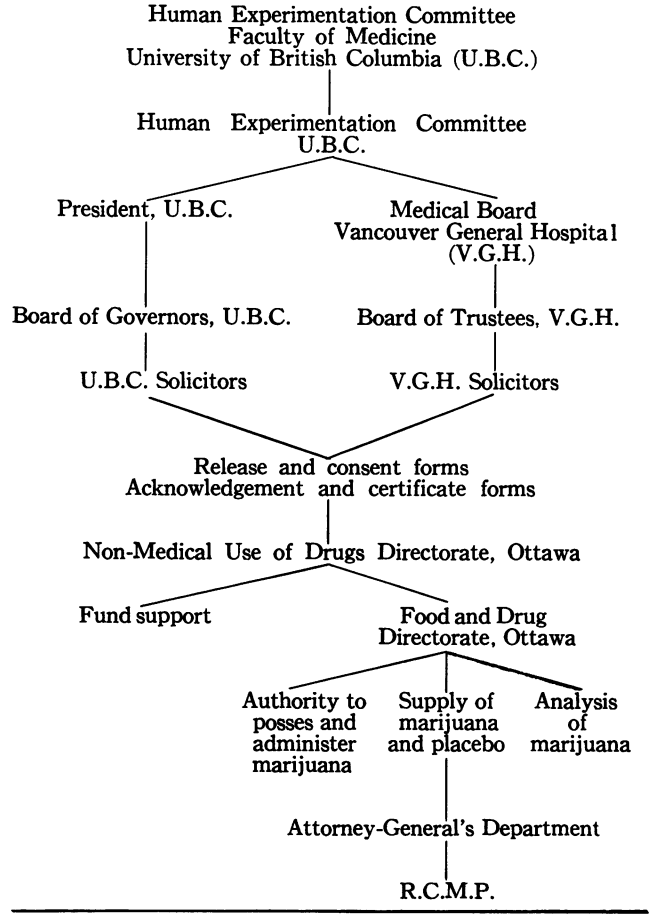
The volunteers were then tested with the Wechsler Adult Intelligence Scale and the Minnesota Multiphasic Personality Inventory. In addition, a questionnaire was completed. The psychological test and questionnaire results will be reported separately.

Volunteers were asked to refrain from using psychoactive drugs for one week prior to the experimental session and during the course of the experiment.

Background characteristics of subjects

The project population consisted of 81 volunteers, 38 men and 43 women. The distribution among the experimental conditions for the low- and high-dose levels is presented in Table II. Mean age was 22.51 years (S.D. 2.81, range 19 to 31). Educational level of the population was as follows: high school — 7%; 1 year of university — 19%; 2 to 4 years of university —

Table I
Channels for initiating research on marijuana



46%; bachelor's degree — 17%; master's degree — 4%; and doctorate or medical degree — 7%. This is a highly educated group, the large majority being university trained and 28% having university degrees. Occupation was classified into the following four categories: post-secondary students — 60%; professional — 10%; semi-professional — 4%; service, technical and clerical — 11%; and skilled and semi-skilled — 15%. The majority of the volunteers were post-secondary students. Of the group, 74% were single, 18% married and 8% divorced, separated or living common-law.

Experimental design and examination procedure

For the neuropsychological examination and re-examination, subjects were assigned to one of four counterbalanced experimental conditions for the high-dose level of drug: marijuana/marijuana, marijuana/placebo, placebo/marijuana and placebo/placebo. For the low-dose level subjects were assigned to one of three counterbalanced experimental conditions: marijuana/marijuana, marijuana/placebo and placebo/marijuana. The placebo/placebo group was used for high- then low-dose level analyses. For the neurophysiological examination, subjects were assigned to marijuana or placebo experimental conditions for low- and high-dose levels. The neuropsychological and neurophysiological results will be reported separately.

The subjects had been informed during the screening that they would receive either marijuana or placebo, but were unaware of the experimental sequence or the dose. The research assistants may or may not have been aware of the dose level. The examinations were conducted in a comfortable clinical environment.

The examination began directly after the smoking of the marijuana or placebo. After completion of the examination and an appropriate interval of time, the volunteer was seen by a physician and the acknowledgement and certificate form was completed. The volunteer agreed not to drive a vehicle until the following morning and was driven home by taxi. The volunteer phoned in the day following the examination to report on his or her condition. The interval between sessions was approximately one week.

Marijuana and placebo

(a) Source, dose, smoking procedure: The marijuana and placebo used in this project were supplied by the Food and Drug Directorate, Ottawa. Low dose was defined as standardized *Cannabis sativa* labelled as containing 0.69% Δ^9-THC, and high dose as containing 1.3% Δ^9-THC. The batch label regarding percentage of Δ^9-THC was confirmed by Food and Drug laboratory analysis. The batches of standardized cannabis forwarded by Food and Drug with higher percentages of Δ^9-THC were mixed with placebo in order to ensure that a constant (in terms of grams of cigarette) and standard (in terms of milligrams of THC) quantity of marijuana was administered to all subjects. Re-analysis by Food and Drug laboratories confirmed the percentage of Δ^9-THC in low- and high-dose batches used in the research.

The placebo was also provided by the Food and Drug Directorate. The physical characteristics of the placebo were identical to those of the *Cannabis sativa* plant material. Food and Drug laboratory testing of the placebo showed that 1 g. extracted in the normal manner gave a negative result on chemical testing for

Table II
Distribution of male and female subjects in the four experimental conditions

	Marijuana/Marijuana		Marijuana/Placebo		Placebo/Marijuana		Placebo/Placebo	
	M	F	M	F	M	F	M	F
Low dose	4	5	5	4	5	3		
							8	5
High dose	5	8	5	10	6	8		

Table III
Composition of doses of marijuana and placebo

Examination	Dose group	Time of of administration	Cigarette (g.)	Total dose (g.)	Approximate dose Δ^9-THC per cigarette (mg.)	Approximate total dose Δ^9-THC (mg.)
	Marijuana	Initial	0.70	1.05	4.8	7.2
	low	1 hr. later	0.35		2.4	
Neuropsychological	Marijuana	Initial	0.70	1.05	9.1	13.6
	high	1 hr. later	0.35		4.5	
	Placebo	Initial	0.70	1.05	—	—
		1 hr. later	0.35			
	Marijuana	Initial	0.70	0.70	4.8	4.8
	low					
Electrophysiological	Marijuana	Initial	0.70	0.70	9.1	9.1
	high					
	Placebo	Initial	0.70	0.70	—	—

the cannabinols. The placebo, when smoked, smelled and tasted like the marijuana cigarettes made from the unextracted plant material.

Marijuana and placebo were administered in the form of cigarettes of standard size and weight made with a hand-operated rolling machine. Table III summarizes dose levels for the neuropsychological and neurophysiological examinations. Weil, Zinberg and Nelsen[1] reported that the effects of marijuana diminish after 30 to 60 minutes. Truitt[3] subsequently found that THC has a half-life of roughly 30 minutes in man. A reinforcing dose of marijuana was accordingly included at the end of the first hour in order to maintain a more consistent level of "high" throughout the examination.

In order to deal with the problem of quantification in delivery of smoked marijuana, the smoking was standardized. As has been pointed out by Manno *et al*,[4] approximately 50% of the total THC content of the cigarette is delivered to the subject, provided the butt is fully smoked. The smoking of marijuana and placebo was standardized and timed with a stopwatch as follows: subject inhaled smoke (forced) for 3 seconds, inhaled air for 1 second (to clear mouth of smoke), held breath for 15 seconds, exhaled and rested for 15 seconds; this procedure was followed until the cigarette was completely smoked. It took approximately 10 minutes to smoke a 0.7 g. cigarette, including the "roach" (butt of cigarette).

Comparison of findings in studies assessing psychological effects is possible only if the potency of the marijuana and the smoking procedure are specified. Reporting to date has been variable, and potency of marijuana is seldom confirmed by independent analysis. When investigators have been more precise in reporting dosage levels, the percentage of Δ^9-THC has been variable, regardless of the route of administration. Studies reporting on Δ^9-THC delivered by smoking have specified amounts of 4.5 and 18 mg.,[1] 3.9 and 6.3 mg.,[5] 2.5 and 5.0 mg.,[4] 5 mg.[6] and 7.5 and 22.5 mg.[7] Le Dain,[8] after reviewing the literature, concluded that in North America most users smoke less than 10 mg. Δ^9-THC to get "stoned". In the four studies conducted by Le Dain and subsequently included in the Commission Report, doses ranged from 0.7 to 6.8 mg. Studies reporting on oral doses have specified amounts of 32 mg.,[9] 20, 40 and 60 mg.,[10] 20 mg.,[11] and 8 to 16 mg.[12] The dose levels in the present study of 4.8 and 9.1 mg. Δ^9-THC administered initially, followed by 2.4 and 4.5 mg. one hour later, are modest in comparison with those of some of the studies but high in comparison with others.

(b) Subjective evaluation of marijuana and placebo: At the conclusion of each experimental session the subject was asked to rate the "high" experienced during the session with previous "high" states, on a scale of 0 to 10, 0 indicating no effect and 10 indicating maximal effect (Table IV). In comparing the subjective impressions of volunteers who smoked low doses of marijuana with those who smoked high doses, the following conclusions emerge (based on average ratings and distribution among no effect, minimally high, moderately high and very high categories): (1) there was generally a positive relationship between dose level and subjective rating of extent of "high"; (2) subjective ratings were related to low- and high-dose levels when marijuana was administered initially or when marijuana was smoked in both sessions; (3) the volunteers did not discriminate between low and high doses when marijuana administered in the second session was preceded by placebo in the initial session. In comparing the subjective impressions of low- and high-dose marijuana conditions with placebo conditions, the following conclusions emerge (based on average ratings and distribution among no effect, minimally high, moderately high and very high categories): (1) placebo during the second session, preceded by placebo during the initial session, was misidentified as such by 54% (moderately high and very high) of the volunteers assigned to this condition; (2) placebo administered initially was not identified as such by either low- (43%) or high- (41%) dose groups; (3) misidentification by low- (11%) and high- (13%) dose groups was, however, infrequent when placebo was administered during the second session and preceded by marijuana in the initial session.

These findings reflect the importance of learned ex-

Table IV
Subjective evaluation of effects of marijuana and placebo

	Low dose					High dose					Placebo
Subjective rating	Marijuana 1st session	Marijuana 2nd session (marijuana 1st)	Marijuana 2nd session (placebo 1st)	Placebo 1st session	Placebo 2nd session (marijuana 1st)	Marijuana 1st session	Marijuana 2nd session (marijuana 1st)	Marijuana 2nd session (placebo 1st)	Placebo 1st session	Placebo 2nd session (marijuana 1st)	Placebo 2nd session (placebo 1st)
	n = 18	n = 9	n = 8	n = 21	n = 9	n = 28	n = 13	n = 14	n = 27	n = 15	n = 13
No effect (0)	0	0	0	3 (14)	7 (78)	0	1 (8)	1 (7)	7 (26)	7 (47)	3 (23)
Minimally high (1 – 2)	1 (6)	0	0	9 (43)	1 (11)	0	0	1 (7)	9 (33)	6 (40)	3 (23)
Moderately high (3 – 6)	6 (33)	3 (33)	3 (37)	7 (33)	1 (11)	6 (21)	2 (15)	2 (14)	8 (30)	2 (13)	6 (46)
Very high (7 – 10)	11 (61)	6 (67)	5 (63)	2 (10)	0	22 (79)	10 (77)	10 (72)	3 (11)	0	1 (8)
Average rating	6.5	6.7	7.2	2.8	.66	7.8	7.3	7.0	2.5	1.2	2.8

Percentage in parentheses

pectancies, set and attitude, as well as prior experience with the drug. For example, the highest incidence of misjudgment in the placebo condition might have been due to an expectancy by the volunteers that they would receive one drug and one placebo experience. Differences in discrimination in the other two experimental conditions might have been due to the presence or absence of a prior laboratory experience with marijuana. The findings of this study are consistent with those of Manno *et al*[4] and Meyer *et al*[13] who also found that subjects were unable to differentiate placebo from marijuana. Jones,[14] in administering marijuana followed by placebo, found that many subjects rated their subjeetive level of intoxication after smoking placebo as identical to that after smoking marijuana.

No distinctive trend was noted in comparing the subjective ratings of males as compared with females. Reanalysis of the data, excluding subjects who had used other psychoactive agents in addition to marijuana or hashish, produced approximately the same results. From the results of the present study, we conclude that the placebo prepared by the Food and Drug Directorate meets specifications for a control group agent in marijuana research.

(c) Subjective evaluation of effects: The subjects spent approximately five minutes at the conclusion of each session dictating an account of their reactions to the marijuana or placebo experience. Subjective effects reported by 17 volunteers who were administered low doses of marijuana and 24 volunteers who were administered high doses* during the initial session were categorized in terms of feeling state, what the volunteer would like to do now, and unusual experiences. Statements by these volunteers regarding feeling state were categorized as positive (1 — happy, content, relaxed; 2 — increased sensory awareness with a pleasant connotation; and 3 — fatigued but content) for 71% of the low- as well as the high-dose group, and as negative (1 — anxious, suspicious; 2 — confused thinking, difficulty in concentration and verbalization; and 3 — fatigued but not content) for 29% of both groups. Rank order of statements regarding what the volunteers would like to do now was as follows for the low-dose group: do something passive, do something active, eat, do something artistic or musical, and unusual. For the high-dose group, the rank order was: do something passive, eat, do something active, do something artistic or musical, and unusual.

Statements regarding unusual experiences were categorized in terms of regression, suspiciousness and projection, somatic references, somatic delusions and delusions. The incidence of unpleasant experiences was high for both the low- (47%) and high- (46%) dose groups; the more striking experiences during the acute intoxication stage reflect abnormal mental content. The abnormal mental content was transient and subsided shortly after the termination of the session. The relative isolation of the volunteer (only one examiner was present during the examination procedure) and the dose of marijuana administered may have contributed to the high incidence of unpleasant experiences, including the frank abnormal content noted.

*Data were not obtained on one volunteer of the low-dose group and four volunteers of the high-dose group.

The presence of adverse effects including hallucinations, impaired mental processes and high anxiety during marijuana intoxication have been documented by others.[15,16] The unresolved question is the relative incidence of usual as compared with adverse effects during marijuana intoxication. The present study suggests that unusual or adverse effects are quite frequently encountered, particularly in laboratory settings. Le Dain[8] confirms that researchers have reported acute reactions under laboratory conditions using doses exceeding 10 mg. $\triangle^9$-THC.

(d) Subjective evaluation of effects the following day: Analysis of the verbal statements (taken over the phone the morning after the initial marijuana session) of 18 volunteers in the low-dose group and 28 in the high-dose group, revealed the following: 82% of the low-dose group and 75% of the high-dose group felt fine and had returned to *status quo ante;* 6% (one volunteer) and 14% (four volunteers), respectively, of the low- and high-dose groups mentioned feeling fatigued; 6% and 4%, respectively, of the low- and high-dose groups reported headaches; and 6% and 7% (two volunteers), respectively, of the low- and high-dose groups felt "slightly high". These data suggest that residual effects the next morning are not infrequent, such effects having been noted by 22% of the sample (17% of the low-dose group and 25% of the high-dose group).

The author wishes to express his appreciation to: A. M. Marcus, M.D., Associate Professor and Head, Division of Forensic Psychiatry, Department of Psychiatry, U.B.C.; M. Low, Ph.D., M.D., Associate Professor (Neurology), Department of Medicine, U.B.C., and Head, EEG Department, Vancouver General Hospital; H. Saunders, Ph.D., Associate Professor, Department of Pharmacology, U.B.C.; C. Fibiger, Ph.D., Post-Doctoral Fellow, Department of Psychiatry, U.B.C.; B. Simpson, R.N. and H. Hoodless, B.Sc., research assistants, Division of Psychology, Department of Psychiatry; the Health Sciences Centre Hospital, U.B.C. and the Vancouver General Hospital, for their cooperation and for providing the necessary research facilities.

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Retrospect

Dangerous drugs

From one who has made a close study of this subject we are told that in Canada and the United States the illicit use of opium, morphine, cocaine and heroin is becoming an international calamity. Rarely a day passes but one reads in our press of an increasing number of addicts and pedlars who come before our magistrates for offences against the Opium and Drugs Act. For the 12 months ending March 31st, 1922, the Federal Government alone prosecuted 23 doctors, 11 druggists, four veterinary surgeons, 165 illicit dealers and 634 Chinamen, making a total of 835 convictions. These figures do not include provincial and municipal convictions. The municipal convictions for Vancouver in 1921 were 858, and in Montreal for the 11 months of 1922, 646. The estimated number of drug addicts in Canada and the United States is 2,000,000 . . . .

Provision must be made whereby those convicted as addicts may be treated not so much as prisoners, but as people diseased, in the almost forlorn hope that some may be permanently cured, and with the knowledge that in confining the addict they are to some extent preventing the making of others, and certainly suppressing crime, for 85% of narcotic prisoners have criminal records . . . .

The experience of the clinic recently established and now discontinued in New York City, has conclusively proven that the so-called ambulatory or slow reduction method of cure was practically useless . . . .

It has on the other hand been demonstrated that the sudden withdrawal method will cure these unfortunates. — A. K. Haywood: Editorial. Can Med Assoc J *13: 54, 1923.*